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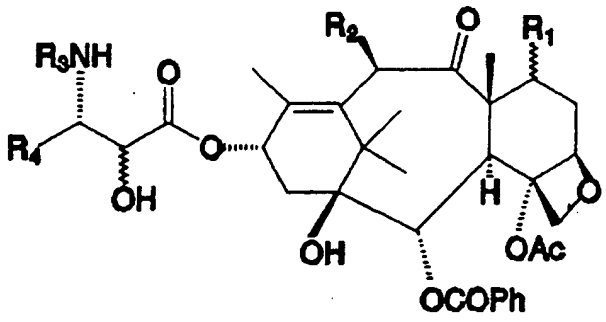
(54) Title: TAXANE DERIVATIVES

(57) Abstract

Taxane derivatives modified at 7-position of the taxane derivative skeleton (taxol numbering) of formula (I) wherein R_1 is N_3, CN, 1H-tetrazol-5-yl, or $-NR_7R_8$ and R_2, R_3, R_4, R_7 and R_8 are organic residues, are endowed with anti-tumor activity.



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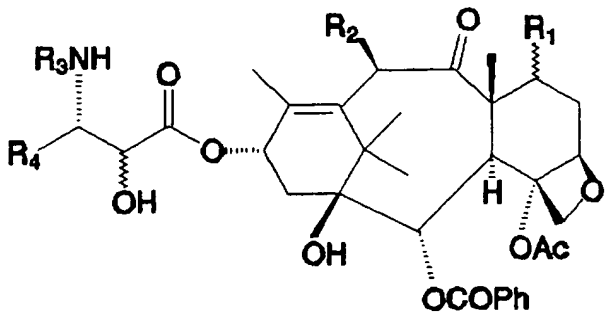
TAXANE DERIVATIVES

The present invention is directed to new taxane derivatives endowed with antitumor activity, to a process for their preparation and to pharmaceutical compositions containing them.

The taxane family of diterpenes includes Paclitaxel (also named taxol in several publications), isolated and characterized from an extract of bark of Taxus brevifolia L., and Cephalomannine (see J.Chem.Soc. Chem.Comm. 102, 1979); other taxane analogues are also known and were prepared by semisynthesis starting from 10-deacetyl baccatin III, extracted from the needles of Taxus baccata L. (see Wani et al., J.Am.Chem.Soc. 93, 2325 , 1971; Lovelle et al., Proc.Am.Assoc.Cancer Res. 31, 417, 1990). Particularly, taxol is a very potent anticancer drug and is already applied with success to the treatment of platinum- resistant ovarian cancer. Nevertheless there is a continuous need for more potent compounds having the broadest possible spectrum of activity on different cancer types.

The present invention provides taxane derivatives modified at the 7-position of the taxane skeleton (taxol numbering). More especially, the invention provides taxane derivatives of formula I:



I

wherein R_1 represents azido, cyano, 1H-tetrazol-5-yl or a residue of formula NR_7R_8 wherein R_7 and R_8 independently represent hydrogen or a C_1-C_6 alkyl, C_1-C_8 alkanoyl or C_7-C_{11} aroyl group;

R_2 represents a hydrogen atom, hydroxy group or a group of formula -OCOR', -OR', -OSO_2R', -OCONR'R", -OCONHR, or -OCOOR' wherein R' and R'' each independently represent C_1-C_6 alkyl, preferably methyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl, C_2-C_6 alkynyl or a phenyl group, optionally substituted with one, two or three substituents which may be the same or different and which are selected from a halogen atom, C_1-C_6 alkyl, C_1-C_6 alkoxy and -CF_3 groups;

R_3 is -COR''' or -COOR''' wherein R''' represents C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl, C_2-C_6 alkynyl or a phenyl group, optionally substituted with one, two or three substituents which may be the same or different and which are selected from a halogen atom, C_1-C_6 alkyl, C_1-C_6 alkoxy and -CF_3 groups; and

R_4 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl or a radical of the formula -W-R_x in which W is a bond, C_2-C_6 alkenediyl or -$(CH_2)_n$- where n is from 1 to 6 such as from 2 to 4 and R_x is naphthyl, phenyl or heteroaryl optionally substituted with one, two or three substituents which may be the same or different and which are selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen and -CF_3 groups, or a pharmaceutically acceptable salt thereof. Preferably, R''' represents phenyl, tert-butyl, 1-methyl- 1-propenyl or n-pentyl; more preferably phenyl.

Preferably R_4 is phenyl.

The wavy lines indicate that the hydroxy group at the

2'-position and the substituent at the 7-position may be in the α or β configuration, or both, i.e. a mixture of stereoisomers is present.

A C_1-C_6 alkyl group is a straight or branched alkyl group, preferably a C_1-C_4 alkyl group such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl. A C_2-C_6 alkenyl group is a straight or branched alkenyl group, preferably á C_2-C_5 alkenyl group e.g. vinyl, allyl, crotyl, 2-methyl-1-propenyl, 1-methyl-1-propenyl, butenyl or pentenyl. A C_3-C_6 cycloalkyl group is a saturated carbocyclic group of 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, preferably cyclohexyl.

A halogen is preferably fluorine, chlorine, bromine or iodine.

A heteroaryl group is preferably a 3- to 6-membered, saturated or unsaturated heterocyclyl ring which contains at least one, for example 1, 2 or 3, heteroatoms selected from O, S and N and which is optionally fused to a second 5- or 6-membered, saturated or unsaturated heterocyclyl group containing one or more, for example 1, 2 or 3, heteroatoms or to a cycloalkyl group or to an aryl group. The 3- to 6- membered heterocyclyl ring may be a 3-, 4-, 5- or 6- membered such ring. A cycloalkyl group is generally a said C_3-C_6 cycloalkyl group. An aryl group is generally phenyl (Ph) or naphthyl.

Examples of heterocyclyl groups are pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl,thienyl, furyl, aziridinyl,

oxiranyl, azetidinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyranyl, pyridazinyl, benzothienyl, benzothiazolyl, benzoxazolyl, isobenzofuranyl, benzofuranyl, chromenyl, indolyl, indolizinyl, isoindolyl, cinnolinyl, indazolyl and purinyl.

A C_2-C_6 alkenediyl chain can be a straight or branched alkenediyl preferably a C_2-C_4 alkenediyl chain such as -CH=CH-, -CH=CH-CH_2- or -CH(CH_3)-CH=CH-. A C_2-C_6 alkynyl group can be a straight or branched alkynyl group preferably a C_2-C_4 alkynyl group such as ethynyl, propargyl, 1-propynyl, 1-butynyl or 2-butynyl. A C_7-C_{11} aroyl group is intended to include benzoyl or naphthoyl residues.

A C_1-C_6 alkoxy group can be a straight chain or branched alkoxyl group, preferably a C_1-C_4 alkoxy group such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy or tert-butoxy. A C_1-C_8 alkanoyl group can be a straight chain or branched alkanoyl group, preferably a C_1-C_5 alkanoyl group such as methanoyl (Ac), ethanoyl, n-propanoyl, isopropanoyl, n-butanoyl, tert-butanoyl or n-pentanoyl. The pharmaceutically acceptable salts include the hydrochloride salt, the hydrobromide salt and the sulphate salt.

Preferred compounds of the invention are the taxane derivatives of formula I wherein R_1 represents azido, cyano, 1H-tetrazol-5-yl or a residue of formula NR_7R_8 wherein R_7 and R_8 independently represent hydrogen or a C_1-C_4 alkyl, C_1-C_5 alkanoyl, benzoyl or naphthoyl group;

R_2 represents a hydrogen atom, hydroxy group or a group of formula -OCOR', -OR', -OSO_2R', -OCONR'R", -OCONHR, or -OCOOR' wherein R' and R'' each independently represent C_1-C_4 alkyl, C_2-C_5

alkenyl, C_3-C_6 cycloalkyl, C_2-C_4 alkynyl or a phenyl group optionally substituted with one, two or three substituents which may be the same or different and which are selected from a halogen atom, C_1-C_6 alkyl, C_1-C_4 alkoxy and -CF_3 groups;

R_3 is -COR''' or -COOR''' wherein R''' represents C_1-C_4 alkyl, preferably methyl, C_2-C_5 alkenyl, C_3-C_6 cycloalkyl, C_2-C_4 alkynyl or a phenyl group optionally substituted with one, two or three substituents which may be the same or different and which are selected from a halogen atom, C_1-C_4 alkyl, C_1-C_4 alkoxy and -CF_3 groups; and

R_4 is C_1-C_4 alkyl, C_2-C_5 alkenyl, C_3-C_6 cycloalkyl or a radical of the formula -W-R_x in which W is a bond, C_2-C_4 alkenediyl or -$(CH_2)_n$- where n is from 2 to 4 and R_x is naphthyl, phenyl or heteroaryl optionally substituted with one, two or three substituents which may be the same or different and which are selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen and -CF_3 groups;

or a pharmaceutically salt thereof.

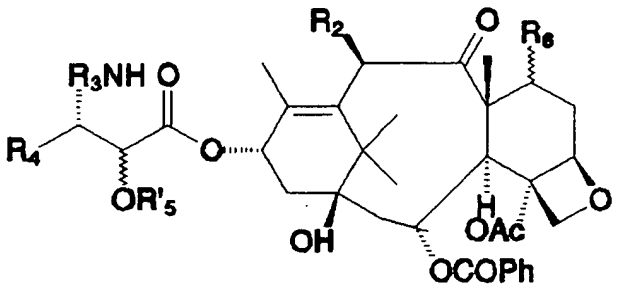
Preferably R' and/or R" is methyl in a taxane derivative of formula I. Preferably R''' is phenyl, tert-butyl, 1-methyl-1-propenyl or n-pentyl. Preferred compounds of the invention are: 7-deoxy-7-epi-azido-taxol, 7-deoxy-7-epi-amino-taxol, 7-deoxy-7-cyano-taxol and 7-deoxy-7-(1H-tetrazol-5-yl)-taxol.

The present invention also provides a process for the preparation of taxane derivatives of formula **I**, as above defined, or a pharmaceutically acceptable salt thereof. In fact, structures of formula **I** can be obtained by a substitution process from a taxane derivative having a suitable leaving group at the

7-position (like triflate, mesylate, tresylate, etc.) and with an optional hydroxy protecting group at the 2'-position (like the acetyl group).

Accordingly, the present invention provides a process for preparing a taxane derivative of formula I or a pharmaceutically acceptable salt thereof, the process comprising

(a) carrying out a substitution reaction with an azide or cyanide salt or a derivative thereof on a taxane derivative of formula II:



(II)

wherein R_2, R_3 and R_4 are as defined above, R'_5 is a hydrogen atom or a hydroxy protecting group R_5 and R_6 is a leaving group, thereby to form a taxane derivative having at the 7-position an azido, cyano or 1H-tetrazol-5-yl group;

(b) optionally reducing the said 7-azido derivative and, if desired, derivatizing the resultant 7-amino taxol to give thereby a taxane derivative of formula II where the leaving group R_6 is replaced by a residue of formula NR_7R_8 where R_7 and R_8 are as defined above;

(c) optionally reacting the said 7-cyano derivative with an

appropriate azide to give the corresponding 7-(1H-tetrazol-5-yl) derivative;

(d) removing, if necessary, the said hydroxy protecting group R_5; and

(e) optionally salifying the resulting taxane derivative of the formula I to form a pharamceutically acceptable salt thereof.

The leaving group R_6 can for example be CH_3SO_2O-, CF_3SO_2O-, $CF_3CH_2SO_2O$- or another suitable leaving group. R_5 may be -$COCH_3$, -$COCH_2Ph$, -$COCH_2CH=CH_2$, Et_3Si-, $(i\text{-}Pr)_3Si$-, t-$BuMe_2Si$-, t-$BuPh_2Si$- or another suitable hydroxy protecting group.

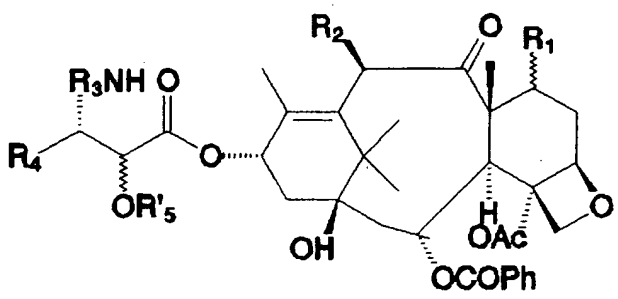
The substitution reaction at the 7-position is typically achieved by reacting a compound of formula **II** with an azide or cyanide ion. The azide is typically sodium azide. The cyanide is typically potassium cyanide. The reaction may be performed in aprotic dipolar solvents, e.g. dimethylformamide (DMF), dimethyl sulfoxide (DMSO) and the like, as well as in phase-transfer catalysis conditions in the presence of a quaternary ammonium salt (for example tricaprylylmethylammonium chloride (Aliquat 336)) and in an apolar organic solvent (for example toluene, benzene, dichloromethane, chloroform, etc). The reaction temperature may vary from 0°C to 120°C.

The reduction of the 7-azido group may be carried out by heterogeneous catalytic hydrogenation (using for example palladium on charcoal) or by means of the Staudinger reaction (triphenyl phosphine in a solvent mixture like tetrahydrofuran (THF)/water). The amino derivatization may be carried out using literature methods; for example reductive alkylation or acylation.

The reaction of the 7-cyano derivative to give a tetrazolyl derivative can be performed using literature methods, for example with trialkyltin azide in toluene.

The removal of the hydroxy protecting group R_5 can be carried out under standard conditions such as hydrolysis or hydrogenolysis or utilizing tetrabutylammonium fluoride for silyl groups. When the protecting group is acetyl, it may be removed by treatment with sodium bicarbonate in $MeOH/H_2O$ or with diethylamine in methanol. The separation of the isomers which are α and β configuration at the 2'- and 7-positions may be carried out by analogy with known methods.

Taxane derivatives of formula III wherein R_1, R_2, R_3, R_4 and R_5 are as defined above are novel and within the scope of the present invention.



(III)

A process for the preparation of taxane derivatives of formula III comprises:

(a) carrying out a substitution reaction with an azide or cyanide salt or a derivative thereof on a taxane derivative of

formula II as defined above, thereby to form a taxane derivative having at the 7-position an azido, cyano or 1H-tetrazole-5-yl group;

(b) optionally reducing the said 7-azido derivative and if desired, derivatizing the resultant 7-amino taxol to give thereby a taxane derivative of formula II where the leaving group R_6 is replaced by a residue of formula NR_7R_8 where R_7 and R_8 are defined as above;

(c) optionally reacting the said 7-cyano derivative with an appropriate azide to give the corresponding 7-(1H-tetrazol-5-yl) derivative.

The taxane derivatives of formula **II** are either known compounds (for example the mesylate of formula **II**, where R_3 is -CO-phenyl, R_4 is phenyl, R_6 is $-OSO_2CH_3$, R_2 is O-acetyl and R_5 is acetyl [see J.Nat.Prod.51,298 (1988)]), or may be prepared from known compounds using established methods. For instance compounds of formula **II** can be used as starting materials where R_3 is -CO-phenyl, R_4 is phenyl, R_6 is hydroxy, R_2 is O-acetyl and R_5 is acetyl [see Bioch.Bioph.Res.Comm.124,329 (1984) or Journal.Nat. Prod.49,665-9(1986)], or where R_3 is -CO-phenyl, R_4 is phenyl, R_6 is hydroxy, R_2 is O-acetyl and R_5 is $COCH_2Ph$ [see Tetrahedron 49,2805(1993) or Tetr.Lett. 34,6845 (1993)] or trimethylsilyl. These known starting compounds can be activated, for example, using mesyl or tresyl chloride or triflic anhydride, in bases such as pyridine at reflux temperature, and then deprotected to give compounds of the formula II wherein R'_5 is a hydrogen atom.

BIOLOGICAL ACTIVITY

The cytotoxic activity of the compounds has been evaluated on B16-F10 murine melanoma cell line which was responsive to taxol. The mode of action of the compound was also tested on the tubulin assembly-disassembly assay in comparison with taxol.

In vitro drug sensitivity assay.

Exponentially growing B16-F10 murine melanoma cells were seeded ($2x10^4$/ml) in RPMI 1640 medium supplemented with 10% heat-inactivated fetal calf serum and 2mM glutamine in 24-well plates (Costar). Scaled concentrations of tested compounds were added immediately after seeding. The inhibition of cell growth was evaluated by counting cells with a Coulter counter after 24hrs incubation. For each tested compound concentration triplicate cultures were used. The antiproliferative activity of the tested compounds was calculated from dose-response curves and expressed as IC_{50} (dose causing 50% inhibition cell growth in treated cultures relative to untreated controls).

The results are shown in Table 1.

Microtubule assembly-disassembly assay.

Calf brain tubulin was prepared by two cycles of assembly-disassembly (Shelanski M.L., Gaskin F. and Cantor C.R., Proc.Natl.Acad.Sci. U.S.A. 70, 765-768, 1973) and stored in liquid nitrogen in MAB (0.1 M MES, 2.5 mM EGTA, 0.5 mM MgSO4 0.1 mM EDTA, 0.1 mM DTT pH 6.4). All the experiments were carried out on protein stored for less than 4 weeks. Before each experiment, tubulin was kept 30 min at 4°C. Assembly was monitored by the

method of Gaskinet al. (Gaskin F., Cantor C.R. and Shelanski M.L., J.Molec.Biol. 89, 737-758, 1974).

The cuvette (1 cm path) containing tubulin (1mg/ml) and 1 mM GTP was shifted to 37°C and continuous turbidity measurements were made at 340 nm on a Perkin-Elmer 557 double wavelength, double beam spectrophotometer equipped with an automatic recorder and a thermostatically regulated sample chamber. After 30 minutes, 4 mM $CaCl_2$ was added and depolymerisation was measured for 10 minutes as decreased turbidity. At regular intervals of 15 minutes scaled doses of the tested compounds were added and variations in the turbidity were monitored. Data are expressed as percentage of repolymerization induced by the tested compounds. The results are shown in Table I.

TABLE I

EXAMPLE	TUBULIN ASSEMBLY (%)		CYTOTOXICITY
	0.5γM	5γM	IC_{50} (nM) B16F10
2	n.d.	n.d	26
3	74	169	33
Paclitaxel (reference compound)	39	93	36

n.d.=not determined

The taxane derivatives of formula I are thus antitumor

agents. A human or animal suffering from a tumor may thus be treated by a method which comprises the administration thereto of an effective amount of a taxane derivative of formula I or II according to the invention. The condition of the human or animal may thereby be improved.

Examples of tumors that can be treated are sarcomas, carcinomas, lymphomas, neuroblastomas, melanomas, myelomas, Wilms tumor, leukemias and adenocarcinomas. The taxane derivatives of formulae I and II can be used to treat ovarian cancer, platinum-resistant ovarian cancer, metastatic breast cancer, non-small cell lung cancer, and head and neck cancer.

The invention also provides a pharmaceutical composition which comprises, as active ingredient, a compound of formula I or II according to the invention and a pharmaceutically acceptable carrier or diluent. The composition of the invention is usually prepared following conventional methods and is administered in a pharmaceutically suitable form. Administration can be made by any of the accepted ways for administration of antitumor agents such as intravenous, intramuscular or subcutaneous injection or topical application. For systemic injection the active compound may be, e.g., dissolved in a vehicle consisting of a mixture of polyoxyethylated castor oil (Chremophor EL) 50% and ethanol 50% and then diluted with glucose 5% solution at the desired concentration, or in other pharmaceutically suitable carriers.

The amount of the active compound administered depends on the treated subject, for example on age, weight, sex etc., and also on the severity of the affliction. The method of administration depends on the judgement of the prescribing

physician. A suitable dosage for an average 70 kg person may range from about 0.01g to about 1g per day.

The following Examples illustrate the invention but they are not intended to limit it thereto.

PREPARATION A

7-O-trifluoromethanesulphonyl-2'-O-triethylsilyl-taxol

To a solution of 2'-O-triethylsisyl-taxol (4.32 g, 4.46 mmole), in freshly distilled pyridine (75 ml), cooled at -5°C, trifluoromethanesulphonic anhydride (3.8 ml) was added dropwise. After 1 hour at 0°C, the reaction mixture was kept at room temperature for 3 hours.

The reaction mixture was poured into cold 0.1 N HCl and extracted with ethyl acetate. The organic layer was washed with NaCl (saturated solution), water and dried over Na_2SO_4.

After concentration, the product was isolated as a whitish solid (4.7 g, 96% yield).

PREPARATION B

7-O-trifluoromethanesulphonyl-taxol.

A solution of 7-O-trifluoromethanesulphonyl-2'-O-triethylsilyl-taxol (4.7 g, 4.27 mmole) in tetrahydrofuran (100 ml) and 1N HCl (7.7 ml) was stirred at room temperature for 30'. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with NaCl (saturated solution), water, dried over Na_2SO_4 and concentrated to yield the title product as a whitish solid in quantitative yield.

PREPARATION C

7-O-trifluoromethanesulphonyl-2'-O-acetyl-taxol

To a solution of 2'-O-acetyl taxol (4.3 g, 4.8 mmoles) in pyridine (40 ml) at 0°C, trifluoromethanesulphonic anhydride (4 ml, 23.8 mmole) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 1 hour. The reaction mixture was washed (x3) with 1N HCl, then with water and NaCl (saturated solution), dried over Na_2SO_4 and concentrated. The desired product (4.46 g) was obtained as a whitish solid.

Example 1

2'-Acetyl,7-deoxy,7-epi-azido taxol

(**III**, R_1=α-N_3, R_2=OAc, R_3=-CO-phenyl, R_4=phenyl, R_5=Ac)

A mixture of 2'-acetyl-7-trifluoromethanesulfonyl taxol (84.5mg, 0.082mmol), sodium azide (84.5mg, 1.3mmol), tricaprylylmethylammonium chloride (Aliquat 336) (3 drops) in toluene (6ml) and water (6ml) was heated at 80°C for 4hrs. The reaction mixture was cooled to room temperature, the two layers separated and the aqueous phase extracted twice with toluene. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated to dryness under vacuum. The crude material was purified by flash chromatography on silica gel (eluant: dichloromethane/ethyl acetate 15:1), yielding 37mg (0.04mmol, 50% yield).

TLC (CH_2Cl_2/EtOAc 6:1), R_f=0.34

^{1}H NMR ($CDCl_3$, 400MHz):

1.13 (s,3H,CH_3-16), 1.18 (s,3H,CH_3-17), 1.76 (s,3H,CH_3-19), 1.99 (d,J=1.2Hz,3H,CH_3-18), 2.15, 2.19 (two singlets,6H, CH_3CO-2'+ CH_3CO-10), 2.48 (s,3H,CH_3CO-4), 2.1-2.6 (m,4H, CH_2-6+CH_2-14), 3.77 (dd,J=2.0Hz,J=5.1Hz,1H,H-7), 3.91 (d, J=7.0Hz,1H,H-3), 4.36, 4.44 (d,J=8.2Hz,2H,CH_2-20), 5.08 (dd,J=3.8Hz,J=10.0Hz,1H,H-5), 5.56 (d,J=3.2Hz,1H,H-2'), 5.73 (d,J=7.0Hz,1H,H-2), 6.00 (dd,J=3.2Hz,J=9.4Hz,1H,H-3'), 6.24 (m,1H,H-13), 6.91 (d,J=9.4Hz,1H,NH-4'), 6.92 (s,1H,H-10), 7.3-8.2 (m,15H,three phenyls).

Example 2

7-deoxy, 7-epi-azido taxol

(I, R_1=α-N_3, R_2=OAc, R_3=-CO-phenyl, R_4=phenyl, R_5=H)

A mixture of 2'-acetyl,7-deoxy,7-epi-azido taxol (50mg, 0.054mmoles), methanol(1ml) and diethylamine in methanol (1ml of 1% solution) was stirred at room temperature for 2hrs, then concentrated under vacuum and dissolved in ethyl acetate. The organic solution was washed (x2) with 0.5N hydrochloric acid, with brine, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography, eluting with n-hexane/ethyl acetate 1:1. Obtained 15mg (0.017mmoles, 30% yield) of pure product.

TLC (n-hexane/EtOAc 1:1), R_f=0.35

^{1}H NMR ($CDCl_3$, 400MHz):

1.13 (s,3H,CH_3-16), 1.19 (s,3H,CH_3-17), 1.75 (s,3H,CH_3-19), 1.85 (d,J=1.2Hz,3H,CH_3-18), 2.20 (s,3H,CH_3CO-10), 2.43 (s,3H,CH_3CO-4), 2.2-2.6 (m,4H,CH_2-6+CH_2-14), 3.50 (bs,1H,OH-2'), 3.75 (dd,J=2.1Hz,J=5.0Hz,1H,H-7), 3.93 (d, J=7.0Hz,1H,H-3), 4.34, 4.45 (two doublets,J=8.0Hz,2H,CH_2-20), 4.82 (d,J=2.6Hz,1H,H-2'), 5.02 (dd,J=3.8Hz,J=9.4Hz, 1H,H-5), 5.73 (d,J=7.0Hz,1H,H-2), 5.84 (dd,J=2.6Hz, J=9.1Hz,1H,H-3'), 6.21 (m,1H,H-13), 6.88 (s,1H,H-10), 7.00 (d,J=9.1Hz,1H,NH-4'), 7.3-8.2 (m,15H,three phenyls).

Exampl 3

7-Deoxy-7-epi-amino-taxol

7-Deoxy-7-epi-azido-taxol (mg. 30, 0.034 mmole) was dissolved in ethylacetate (2 ml)

Catalyst 5% Pd/C (35 mg) was added and the reaction mixture subdued to hydrogen atmosphere (48 psi) at room temperature for 72 hours under shaking.

After the filtration and concentration the crude product (27 mg) was purified on preparative silica gel TLC, eluating with n-hexane/ethylacetate 1/1.

The title compound (10 mg, 0.012 mmole, 34% yield) was isolated as a white solid.

R.f ≈ 0.16 (n-hexane/ethylacetate 1/1)

^{1}H-NMR (400MHz, $CDCl_3$)

1.15 (s, 3H, 16), 1.18 (s, 3H, 17), 1.70 (s, 3H, 19), 1.76 (s, 1H, OH-1), 1.79 (d, J=1.5Hz, 3H, 18), 2.1-2.5 (m, 4H, CH_2-14+CH_2-6), 2.19 (s, 3H, CH_3CO-10), 2.46 (s, 3H, CH_3CO-4), 2.89 (d, J=2.9Hz, 1H, 7), 3.45 (bs, 1H, OH-2'), 3.92 (d, J=7.3Hz, 1H,3) 4.32, 4.52 (two doublets, J=8.5Hz, 2H, CH_2-20), 4.80 (d,J=2.6Hz, 1H, 2'), 4.95 (dd, J=5.0 Hz, J=9.5 Hz, 1H,5), 5.74 (d, J=7.3 Hz, 1H,2), 5.83 (dd, J=2.6 Hz, J=9.1 Hz, 1H,3'), 6.21 (m, 1H, 13) 7.02 (d, J=91HZ, 1H, NH-4'), 7.24 (s, 1H, 10), 7.3-8.2 (m, 15H, 3 Ph)

Example 4

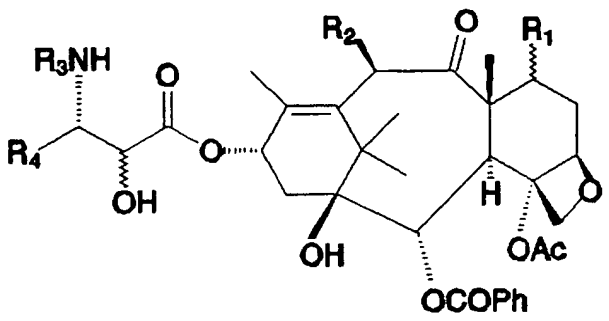
7-deoxy-7-epi-azido taxol

(**I**, R_1=α-N_3, R_2=OAc, R_3=-CO-phenyl, R_4=phenyl, R_5=H)

A solution of 7-O-trifluoromethanesulphonyl taxol (4.3 g), sodium azide (4.3 g) and Aliquat 336(registered mark) (5.18 g) in toluene (360 ml) and water (360 ml) was vigorously stirred at 80°C for 2 hours. The reaction mixture was cooled to room temperature, the organic layer was washed with NaCl (saturated solution), water, dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography on silica gel, eluant CH_2Cl_2/EtOAc 4:1. There were obtained 1.52 g (1.7 mmole, 40% yield) of the title compound, having the same physico-chemical data of that prepared in Example 2.

CLAIMS

1. A taxane derivative of formula I:



I

wherein:

R_1 represents azido, cyano, 1H-tetrazol-5-yl or a residue of formula NR_7R_8 wherein R_7 and R_8 each independently represent hydrogen or a C_1-C_6 alkyl, C_1-C_8 alkanoyl or C_7-C_{11} aroyl group;

R_2 represents a hydrogen atom, hydroxy group or a group of formula -OCOR', -OR', -OSO_2R', -OCONR'R", -OCONHR' or -OCOOR' wherein R' and R" each independently represent C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl, C_2-C_6 alkynyl or a phenyl group optionally substituted with one, two or three substituents which may be the same or different and which are selected from a halogen atom, C_1-C_6 alkyl, C_1-C_6 alkoxy and -CF_3 groups;

R_3 is -COR''' or -COOR''' wherein R''' represents C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl, C_2-C_6 alkynyl or a phenyl group, optionally substituted with one, two or three substituents which may be the same or different and which are selected from a halogen atom, C_1-C_6 alkyl, C_1-C_6 alkoxy and -CF_3 groups; and

R_4 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl or a radical of

the formula -W-R_x in which W is a bond, C_2-C_6 alkenediyl or -$(CH_2)_n$- where n is from 1 to 6 and R_x is naphthyl, phenyl or heteroaryl optionally substituted with one, two or three substituents which may be the same or different and which are selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen and -CF_3 groups, or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R_1 represents azido, cyano, 1H-tetrazol-5-yl or a residue of formula NR_7R_8 wherein R_7 and R_8 independently represent hydrogen or a C_1-C_4 alkyl, C_1-C_5 alkanoyl, benzoyl or naphthoyl group;

R_2 represents a hydrogen atom, hydroxy group or a group of formula -OCOR', -OR', -OSO_2R', -OCONR'R", -OCONHR, or -OCOOR' wherein R' and R'' each independently represent C_1-C_4 alkyl, C_2-C_5 alkenyl, C_3-C_6 cycloalkyl, C_2-C_4 alkynyl or a phenyl group optionally substituted with one, two or three substituents which may be the same or different and which are selected from a halogen atom, C_1-C_4 alkyl, C_1-C_4 alkoxy and -CF_3 groups;

R_3 is -COR''' or -COOR''' wherein R''' represents C_1-C_4 alkyl, C_2-C_5 alkenyl, C_3-C_6 cycloalkyl, C_2-C_4 alkynyl or a phenyl group optionally substituted with one, two or three substituents which may be the same or different and which are selected from a halogen atom, C_1-C_4 alkyl, C_1-C_4 alkoxy and -CF_3 groups; and

R_4 is C_1-C_4 alkyl, C_2-C_5 alkenyl, C_3-C_6 cycloalkyl or a radical of the formula -W-R_x in which W is a bond, C_2-C_4 alkenediyl or -$(CH_2)_n$- where n is from 2 to 4 and R_x is naphthyl, phenyl or heteroaryl optionally substituted with one, two or three substituents which may be the same or different and which are

selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen and -CF_3 groups, or a pharmaceutically acceptable salt thereof.

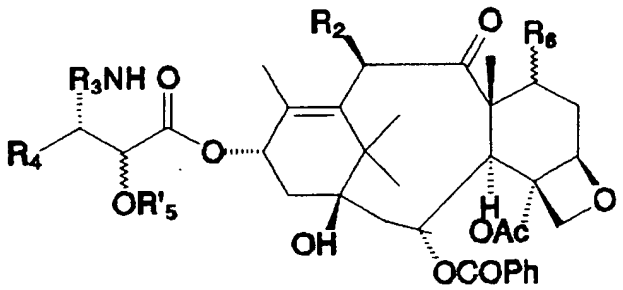
3. A compound according to claim 1 or 2 wherein R' and/or R'' is methyl.

4. A compound according to any one of the preceding claims wherein R''' is phenyl, tert-butyl, 1-methyl-1-propenyl or n-pentyl.

5. A compound according to claim 1 which is selected from 7-deoxy-7-epi-azido-taxol, 7-deoxy-7-epi-amino-taxol, 7-deoxy-7-cyano-taxol, 7-deoxy-7-(1H-tetrazol-5-yl)-taxol.

6. A process for preparing a taxane derivative of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof, which process comprises:

(a) carrying out a substitution reaction with an azide or cyanide salt or a derivative thereof on a taxane derivative of formula **II**:



(II)

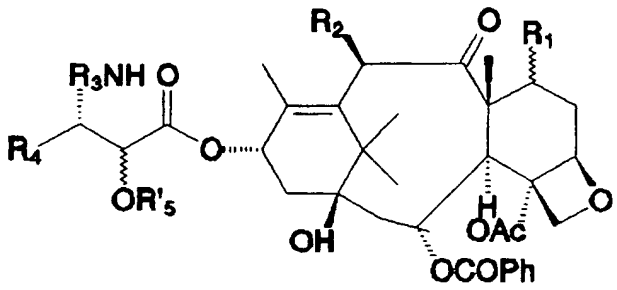
wherein R_2, R_3 and R_4 are as defined in claim 1, R'_5 is hydrogen or a hydroxy protecting group R_5 and R_6 is a leaving group, thereby to form a taxane derivative having at the 7-position an azido, cyano or 1H-tetrazol-5-yl group;

(b) optionally reducing the said 7-azido derivative and,

if desired, derivatizing the resultant 7-amino taxol to give thereby a taxane derivative of formula II where the leaving group R_6 is replaced by a residue of formula NR_7R_8 where R_7 and R_8 are defined in claim 1;

(c) optionally reacting the said 7-cyano derivative with an appropriate azide to give the corresponding 7-(1H-tetrazol-5-yl) derivative;

(d) removing, if necessary, the said hydroxy protecting group R_5 from the resulting intermediate of formula III:



(III)

wherein R_1 is as defined in claim 1 and R_2, R_3, R_4 and R'_5 are as defined above; and

(e) optionally salifying the resulting taxane derivative of the formula I to form a pharmaceutically acceptable salt thereof.

7. A compound of the formula III as defined in claim 6.

8. A process for preparing a compound of the formula III as defined in claim 6, which process comprises

(a) carrying out a substitution reaction with an azide or cyanide salt or a derivative thereof on a taxane derivative of formula II as defined in claim 6, thereby to form a taxane

derivative having at the 7-position an azido, cyano or 1H-tetrazol-5-yl group;

(b) optionally reducing the said 7-azido derivative and, if desired, derivatizing the resultant 7-amino taxol to give thereby a taxane derivative of formula II where the leaving group R_6 is replaced by a residue of formula NR_7R_8 where R_7 and R_8 are defined in claim 1.

(c) optionally reacting the said 7-cyano derivative with an appropriate azide to give the corresponding 7-(1H-tetrazol-5-yl) derivative.

9. A phamaceutical composition which comprises a taxane derivative of the formula I as defined in any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable diluent or carrier.

10. A taxane derivative of formula I as defined in any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof for use as an antitumor agent.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D305/14 A61K31/335 C07D405/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,94 13655 (UPJOHN) 23 June 1994 see page 60 - page 107; claims; example 20 ---	1,2,6-10
P,X	WO,A,95 20582 (UPJOHN) 3 August 1995 see claims 1,14 ---	1,2,6-10
P,X	TETRAHEDRON LETTERS, vol. 36, no. 17, 24 April 1995 OXFORD GB, pages 2901-2904, XIAN LIANG ET AL. 'SYNTHESIS AND BIOLOGICAL EVALUATION OF PACLITAXEL ANALOGS MODIFIED IN RING C.' see page 2901 - page 2903 -----	1,2

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 March 1996	11.03.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Francois, J

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		CN-A-	1095377	23-11-94
WO-A-9520582	03-08-95	AU-B-	1680695	15-08-95